Full title:
A Multicenter Randomized Controlled Trial Assessing the Efficacy of Antimicrobial Prophylaxis for Extracorporeal Shock Wave Lithotripsy on Reducing Urinary Tract Infection

Brief Title:
Antibiotic Prophylaxis Before Shock Wave Lithotripsy (APPEAL)

1. Objectives & Specific Aims

The lifetime risk of developing nephrolithiasis has been reported between 1-15%, with a prevalence of approximately 5% in North America. SWL is a very common first line treatment for ureteral and renal calculi. One of its benefits is that it has few complications. However, infection remains an important complication of the procedure. Because of this risk the American Urological Association recommends pre-SWL antibiotics for all patients. However, this approach is controversial because studies to date are of poor quality and there is concern over antibiotic resistance. Therefore the European Association of Urology recommends only selective use of antibiotics pre-SWL. To resolve this conflict and establish the most appropriate strategy for Ontarians, we propose to perform a randomized trial comparing pre-procedure antibiotics to no antibiotics among patients who undergo SWL.

The primary goal of our study is to evaluate the impact of antibiotic prophylaxis on the rate of bacteriuria, symptomatic UTI, pyelonephritis and urosepsis among patients with sterile urine undergoing SWL. Our secondary goal is to determine pre-procedural characteristics that can define patient subgroups with the greatest benefit from prophylactic antibiotics.

We hypothesize that a single dose of intravenous ciprofloxacin immediately prior to SWL will decrease the relative incidence of bacteriuria, symptomatic UTI, pyelonephritis and urosepsis by 60% or greater. Additionally, we anticipate that pre-operative patient and stone characteristics such as age, gender, history of UTI, patient comorbidities, stone size, location, may be predictive risk factors that can be used to optimize patient selection for pre-operative antibiotic use.

To test this hypothesis we propose to conduct a large ($n \geq 1350$), multicenter prospective randomized, blinded, placebo controlled trial (RCT). We recognize that our primary question may be difficult to study due to low rates of symptomatic UTI post-SWL. Therefore we propose to undertake this RCT in two phases. The Vanguard phase, which will consist of up to one fourth of the total study population, will be used to determine feasibility. Feasibility will be assessed in terms of rates of patient recruitment, percent adherence to randomization, percent data completion and percent loss to follow-up. Using pre-defined criteria, if the study is deemed to be feasible without major protocol alterations, the Vanguard phase patients will be included in the larger study. Patient recruitment will then continue until our target population size has been reached. Should the Vanguard phase be unable to demonstrate feasibility, then the available data will be analyzed, which will still provide the largest and most methodologically robust dataset available in the literature at this time.

The results of our RCT, whether positive or negative, will contribute significantly to the existing literature as it will provide the strongest Level 1 evidence available for future meta-analyses and guidelines. If the study results show a benefit to antibiotic use the expected impact on patient care will be to reduce rates of infectious complications. Furthermore, our study will allow for a more selective use of antibiotics as several important predictors of infectious complications will be elucidated through a multivariate analysis. Conversely, a null study will provide the strongest evidence against routine prophylaxis in the literature to date and potentially decrease the unnecessary use of antibiotics among patients undergoing SWL. Consequently, this would represent a cost savings to the healthcare system and may reduce the risk antibiotic resistant bacteria.

2. Background, Rationale & Present State of Knowledge

The lifetime risk of developing nephrolithiasis has been reported between 1-15%[1,-3], with a prevalence of approximately 5% in North America[4]. Recent reviews suggest that the incidence and prevalence of kidney stones are increasing globally[5,6]. Extracorporeal shock wave lithotripsy (SWL) is a preferred treatment for the majority of renal and ureteric calculi[7-9]. One significant advantage of SWL is the relatively low rate of complications. However, infectious complications are among the most common, even among patients with sterile pre-SWL urine cultures. The reported rate of bacteriuria is 8-23% [10,11], symptomatic urinary tract infection (UTI) is 1.4-5.7%[12,13] and urosepsis is 0.1-2.7%[10,11]. These reports have led to considerable interest in the use of prophylactic antibiotics prior to SWL. The American Urological Association (AUA) has recently published a Best Practice Statement on antimicrobial prophylaxis and recommended antibiotic prophylaxis for all patients undergoing SWL, even those with sterile urine. This position was based on evidence from a meta-analysis published by Pearle et al in 1997[13]. In contrast, a more recently published review by Bootsma et al.[14] and a meta-analysis by Lu[15] concluded that there was no role for antibiotic prophylaxis for uncomplicated patients undergoing SWL. This position is further supported by the European Association of Urology (EAU) Guidelines, which recommend selective antibiotic prophylaxis, only for patients with indwelling catheter, nephrostomy tube, or infectious stones[16,17].

The AUA Best Practice Statement on the use of perioperative antibiotics for urological procedures relies heavily on a single meta-analysis published in 1997[13,18] . In their meta-analysis, the results of eight prospective RCTs (n=885)[19-26] and six clinical series (n=597)[27-31] were analyzed. The authors concluded that the use of antibiotic prophylaxis prior to SWL for patients with sterile pre-treatment urine cultures reduces post-SWL UTI rates and may be cost effective. Unfortunately, these trials were highly heterogeneous. The heterogeneity was not formally quantified or accounted for by the authors. All eight RCTs used different antibiotic regiments, lengths of follow-up and definitions of bacteriuria and UTI. Many of the antibiotic regimens used were not common urological practice and are of questionable generalizability[23,25,26]. Additionally, the meta-analysis included two RCTs in which the prophylactic arm received a seven day course of antibiotics and a third trial in which a 48 hour regimen was used[20,22,23]. This in particular may be of concern as the AUA Best Practice Statement recommends antibiotic prophylaxis for 24 hours or less based on this meta-analysis[18]. In our study, we propose to test the standard of a single pre-procedure dose of intravenous ciprofloxacin versus placebo.

Since the publication of Pearle *et al.*'s meta-analysis, there have been two additional RCTs investigating the use of prophylaxis for SWL[32,33]. Beirkens et al. attempted to perform a five arm single blinded RCT, comparing single dose ciprofloxacin 200mg IV, single dose cefuroxime 750mg IV, ciprofloxacin 200mg daily for seven days, Cefuroxime 750 mg on day one and 250 mg for six days, and placebo. A total of 177 patients were recruited (30/41/39/29/38 per group respectively). However, the study was ended after interim analysis failed to reveal any significant difference between placebo and antibiotic groups. Their results show a non-significant difference in symptomatic UTI between antibiotic and placebo groups of 2.0% vs. 3.0% at two weeks, and 1.4% vs. 2.7 % at six weeks. This study could conceivably have addressed important questions regarding the optimal regimen of prophylaxis. Unfortunately, the power of this study to find potential benefit for any given regimen is limited due to the relatively rare occurrence of UTI post-ESWL and the small sample size for the number of treatment arms. A second study by Ghazimoghaddam et al. attempted to randomize 150 patients into 3 arms (septra, nitrofuratoin, no antibiotic). The authors identified rates bacteriuria of 10-14% in each group at two weeks post-SWL and concluded that prophylaxis did not seem to be necessary. Unfortunately this study was also significantly underpowered in particular for a three arm trial [33]. Our proposed study design will avoid this problem by limiting the study groups to prophylaxis

vs. placebo and we propose to recruit a sufficiently large sample size (n≥661 per arm) to detect a 60% relative decrease in incidence of infectious complication with a power of 90% and a p=0.05.

In a recent systematic review of antibiotic use in urologic procedures, Bootsma et al. performed a review of four RCTs regarding antibiotic prophylaxis for SWL[14]. These included three from Pearle *et al.*'s meta-analysis[19,21,24] and the study by Beirkens *et al.*[32] The authors excluded two studies[22,23] as these evaluated 7 day antibiotic treatment regimens rather than prophylaxis. An additional two studies[25,26] were excluded due to incomplete description of methodology and inconsistency between results and conclusions. A small RCT[20] (n=49) was excluded but not commented on by the authors. It is likely that this study did not meet inclusion criteria as it mandated a 48hour antibiotic regimen pre-op and defined bacteriuria as $>10^4$ CFU/ml. In their synthesis of the remaining data Bootsma et al. concluded that the available evidence was of low quality and routine antibiotic prophylaxis was not indicated in SWL.

More recently, a formal meta-analysis of 9 studies was carried out by Lu et al[15]. This meta-analysis included the three trials[19,21,24] common to previous analysis, three trials[20,22,25] which had been excluded from the review by Bootsma et al. and three additional trials[33,34,35]. It is unclear why the authors chose to include the trials previously excluded by Bootsma et al., as each had significant methodological flaws such as incomplete description of methodology[26], 7-day treatment course of antibiotics[23]. It is equally unclear why other trials with similar methodological problems were not included[24,27]. Of the three additional studies, one was new[33] and the other two had either been excluded or not captured in the previous reviews and meta-analysis. In the analysis by Lue et al., the authors report pooled risk ratios with a test of heterogeneity for fever, positive urine culture both (short-term <7days and mid-term>7days) and symptomatic urinary tract infection and the presence of double-J stent separately. The I^2 values for these parameters were 60% for fever, 37% and 49% for short-term and mid-term bacteriuria, 0% for UTI, and 0% for presence of double-J stent. We caution that the I^2 value for the latter two parameters does not imply perfect homogeneity between studies, but is an artifact of the low number of events in any given study. Overall, the variability among I^2 values indicates that there is considerable heterogeneity among studies included in their meta-analysis. Nonetheless, the authors fail to find benefit for antibiotic prophylaxis. Notably, the authors of all 3 reviews and meta-analyses on the topic acknowledge the poor quality of available studies and suggest the need for a large high quality randomized controlled trial.

Despite the poor quality of evidence available, the EAU guidelines on urological infections and on urolithiasis regarding the use of antibiotic prophylaxis for SWL recommend antibiotic prophylaxis only for patients perceived to have increased risk of bacterial burden. These are defined as those with an indwelling catheter, nephrostomy tube, or infectious stones. Therefore, to account for these plausible recommendations, our proposed study will exclude patients with indwelling catheter, nephrostomy tubes or known, or suspected, struvite stones.

Based on the existing literature, a prominent area of concern that emerges is how to define a positive urine culture and how to assess for symptomatic urinary tract infection. Previous studies have used a variety of bacterial concentration cutoffs for the definition of a positive culture[13]. We will use the most common historically accepted definition ($\geq 10^5$ CFU/ml) to define a conservative estimate of bacteriuria for the primary and secondary endpoints of our study[36]. To define a symptomatic UTI we will capture symptoms in two different ways. We will use a predefined questionnaire in a systematic way asking patients to identify both the presence and absence of lower urinary tract symptoms as well as to quantify the magnitude of these symptoms on a scale from 0 to 5. We recognize that the passage of stone debris or presence of stent can cause lower urinary tract symptoms, but believe that appropriate randomization over a sufficiently large cohort will control for this confounder.

In addition we will evaluate the IPSS score as a quality of life measure for lower urinary tract symptoms post-SWL. We believe this is important as symptoms of UTI related to SWL may worsen IPSS scores and correlate to decreased quality of life. It is therefore of benefit to evaluate whether pre-operative antibiotic use can impact on this aspect of patient care. Unfortunately there have not been any systematically validated questionnaires that can be used to diagnose urinary tract infections among men and women. The urinary tract infection symptom assessment questionnaire (UTISA) has been validated to track resolution of UTI symptoms among symptomatic women. However it is not diagnostic nor has it been validated in men[37]. We have chosen to use the IPSS, as it has been widely validated for the description of lower urinary tract symptoms in men[38-40]. It IPSS has also been frequently used to define lower urinary tract symptoms in women is several clinical contexts[41-44]. We recognize that it has not been shown to be useful in the evaluation of bladder outlet obstruction in women[45], a pathology that we are not assessing in our RCT.

3. References

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4. Project Design, Methodology and Analysis

We propose to carry out a two arm, double blind RCT comparing the use of a single dose ciprofloxacin prior to SWL to placebo. This study will be carried out in parallel in multiple sites internationally with the methods center located at the Department of Urology, University of Helsinki and Helsinki University Hospital (Hospital District of Helsinki and Uusimaa), Helsinki, Finland.

The proposed study will be carried out in two phases. The initial Vanguard phase will assess the feasibility of the trial in terms of rates of patient recruitment, percent adherence to randomization, percent data completion and percent loss to follow-up. Pre-defined criteria to determine feasibility will be a rate of randomization of ≥16 patients per week, with 95% adherence to randomization and an overall rate of ≥ 90% data collection at 3 weeks post-SWL, and an overall loss to follow-up of ≤10%. These parameters will be assessed weekly throughout the Vanguard period. This phase of the study will continue until all target parameters have been met for 3 consecutive weeks and a minimum of 200 patients have been randomized. If these parameters are met then the Vanguard phase will interpreted to have demonstrated feasibility and patient recruitment will continue until complete data for ≥1350 patients has been collected. Alternatively, the Vanguard phase may be concluded when a maximum of 300 patients or a six month period from study start date has elapsed or a modification to number of sites accruing may be considered. If the Vanguard phase fails to demonstrate feasibility, and we judge that this indicates that a significant protocol modification is needed we will close the trial and analyze available data. The data would be analyzed in accordance with pre-defined methodology and would be submitted for publication. Importantly, even if the Vanguard phase does not show feasibility, it would still provide the largest cohort of high quality data available in the literature and as such would still be an important contribution to the current state of knowledge.

The study centres, Helsinki University Hospital, University of Western Ontario St Joseph's Hospital, Université de Sherbrooke, Pontifical University Catholic of Campinas, Rede D'Or Sao Luiz, and King Abdulaziz University are each academic institutions with dedicated research staff. We estimate that total of 2000 patients will need to be screened in order to acquire complete data for 1350 patients. Accounting for a 10% dropout, up to 1500 patients may need to be randomized. Eligibility criteria include patients older than 18 years presenting for SWL who do not meet one of the pre-defined exclusion criteria. Exclusion criteria are:

- Pre-SWL urine analysis positive for nitrites
- Pre-SWL urine culture reveals $>10^5$ CFU/ml of bacteria (positive urine culture)
- Taking antibiotics for UTI or other cause
- Suspected struvite stone (based on previous stone analysis, or partial staghorn)
- Presence of nephrostomy tube
- Requiring cystoscopy and ureteral stent insertion on the day of SWL
- Presence of Foley catheter or patient on regular clean intermittent catheterization (CIC)
- Presence of urinary diversion (ie: ileal conduit)
- History of urosepsis prior to SWL
- Known allergic reaction to trial antibiotic
- Previous randomization in this trial

Patients who are eligible for inclusion will then provide written informed consent. Risks and benefits will be discussed with the patient and will include being informed of a low risk of allergic reaction, colonization with antibiotic resistant organisms, and very low risk of developing of *C.Difficile* related diarrhea, or tendon injury. Conversely, the probability of successful SWL is not likely to be

influenced by our intervention. Participants will then fill out a pre-procedure study questionnaire in which baseline and demographic information will be gathered as well as a generic International Prostate Symptom Score (IPSS) questionnaire. Patients will be assigned a randomization number that will correspond to their treatment arm. Block randomization using blocks of 10 will be carried out by a central randomization organization (www.randomize.net) using a computerized algorithm. Only the research pharmacist at each site will have access to the randomization code, which will be made available for un-blinding once statistical analysis is complete. The patient and data analyst will remain blinded to treatment allocation. To ensure patient blinding, the IV solution will be concealed within a opaque paper bag or identical oral placebo and study medication will be manufactured.

Patients routinely undergo neuroleptic anesthesia during SWL at participating centers, as such it is usual care for the patient to have a saline infusion during SWL. The choice of whether or not to administer antibiotics is usually at the discretion of the attending urologist, as there is no established standard of care. For the duration of the study, participants will be mandated to receive treatment in accord with randomization. However the attending urologist will retain the ability to break protocol in accord with their clinical judgment. Any break in protocol will be recorded as such but the data will be analyzed on an intent-to-treat basis. Ciprofloxacin was chosen as the study antibiotic as it is commonly used in everyday practice, has been used in previous RCTs on antibiotic prophylaxis pre-SWL[31] and demonstrates a good sensitivity pattern to community acquired infections. Patients will undergo SWL with a maximum of 3000 shock waves (SW) for kidney stones and up to 4500SW for ureteric stones. Additional clinical parameters such as presence of double J, Stone characteristics and renal insufficiency will be recorded at the time of SWL by the dedicated research staff.

Patients will be asked to provide two urine samples for analysis. The first will be prior to SWL within 1 month of the procedure. On the day of procedure the patient will also complete baseline documentation. After the procedure, patients will complete follow-up documentation and a second urine culture. Urine cultures will be submitted to the laboratory or hospital most convenient for the patient at 7-14 days post-SWL and results will be forwarded to the regional site. We allow the patient to submit a urine culture at their usual laboratory in an effort to minimize the burden for the patient participating in the trial and to facilitate capture of follow-up data. This approach may be essential to capture data from patients referred from an outside institution, which may represent a significant commute. An additional advantage of this approach, in contrast to mandating the use of a central laboratory, is that it may better reflect the usual pattern of patient behavior when seeking follow-up for urinary tract symptoms post-SWL. We recognize that there may be differences in culture protocol between laboratories but we feel that these are more representative of actual practice and as such support the generalizability of the study.

Data acquisition will be continuously monitored, with regular audits to assure that data from patients who have not complied with follow-up are obtained. Patients will be asked to provide a urine sample and complete and mail the follow-up form on post-operative day 7. If the follow-up questionnaire has not been received by post-operative day 10 patients will receive a reminder phone call. A second envelope will be sent containing a requisition for urine culture and follow-up questionnaire when necessary.

Our primary outcome will be a composite endpoint comprised of:

- Positive post-SWL urine culture ($\geq 10^5$ CFU/ ml), symptoms of cystitis (defined as new onset burning sensation or pain with voiding, frequency, urgency), or pyelonephritis or urosepsis (hospital admission with fever ≥38.5 C).

Our secondary outcomes will be:

- Bacteriuria at 7-14 days post-SWL ($\geq 10^5$ cfu/ml)
- Symptoms of cystitis (new onset burning sensation or pain with voiding, frequency, urgency)
- Pyelonephritis or urosepsis (hospital admission with fever ≥38.5C)
- Change in IPSS score at 2 weeks (reported as a numerical value)

We elected to measure a composite endpoint as our primary outcome for several reasons. The decision to combine several outcomes of interest, namely new post-procedure bacteriuria ($\geq 10^5$ CFU/ml), symptomatic cystitis, pyelonephritis and urosepsis, is necessary in order to limit the sample size while maintaining appropriate statistical power. This is due to the relatively rare occurrence of serious infectious complications, such as pyelonephritis and urosepsis[10,11]. Although preventing these complications is of great clinical interest, to study their prevention post-SWL in isolation would require a prohibitively large sample size. Therefore, the use of more common, but less severe, complications such as symptomatic cystitis and bacteriuria as surrogates is appropriate. Furthermore one would expect that if there is beneficial effect of pre-SWL antibiotics then this effect would be in the same direction for each component of our composite endpoint. For example, if there is a decrease in symptomatic bacteriuria among patients in the antibiotic arm one would also expect there to be a decrease in pyelonephritis. This biological coherence is intuitive as bacteriuria is a prerequisite for pyelonephritis. However it is likely that rates of pyelonephritis alone would not be sufficiently high to compare with statistical certainty. It remains important to report component outcomes individually as secondary endpoints to confirm concordance of the effect of the study medication across component outcomes.

Data analysis

Power and sample size calculation

The power calculation for this protocol was performed using Stata v.10.1 (StataCorp, College Station, TX). Reported incidence of bacteriuria, symptomatic UTI and pyelonephritis post-SWL vary greatly[10-13]. Therefore, to estimate the expected incidence of our primary outcome, we used the incidence of bacteriuria reported in the AUA Best Practice Statement on antibiotic prophylaxis[17]. In the AUA statement, patients undergoing SWL in the placebo arm of trials assessing antibiotic prophylaxis had a 5.7% rate of bateriuria as compared to 2.1% among those who received prophylaxis. This represented an absolute difference of 3.6% (a 60% relative risk reduction). Therefore to achieve a power of 90% to find an absolute difference of 3.6% in the occurrence of bacteriuria, with a significance level of $p<0.05$, 661 patients will need to be recruited in each arm for a total of 1,322 patients. Accounting for 10% loss to follow-up, the total required will be 1454, or approximately 1500 patients. Assuming that 25% of patients screened will either refuse to be randomized or will meet one of the pre-defined exclusion criteria, a total of 2000 patients will need to be screened in order to randomize 1500 patients.

Statistical analysis

Once all study data has been collected, we will report the patient characteristics at enrollment, and the primary and secondary outcomes. Comparison between RCT outcomes will be performed using Fisher's exact test for binary outcomes and Student's t-test for continuous outcomes. Lost to follow-up will be accounted for according to intent to treat analysis. Patients who are lost to follow-up will be considered not to have bacteriuria, cystitis, pyelonephritis or urosepsis and a change in IPSS of zero. This will allow us to accomplish the primary objective: to determine the impact of antibiotic prophylaxis on our primary and pre-defined secondary endpoints. We will also perform a univariate and multivariate analysis using a stepwise logistic regression model to assess predictors of our primary

outcome. This will allow us to better characterize the impact of pre-SWL antibiotic use in the context of other known risk factors for UTI.

Strengths and weaknesses of study design

There are several limitations to our proposed trial. The primary criticism may be the use of a composite endpoint as a surrogate for serious infection, which is the most important outcome that we wish to prevent with our study intervention. However, there are a number factors that provide adequate justification for the use of a composite primary endpoint in this study. Firstly, the use of a composite endpoint will improve the study's statistical power thereby reducing the sample size requirement and associated cost and time to do the trial. Secondly, there is a clear biological coherence among the component variables included in the composite outcome. This will facilitate the interpretation of study findings, as a reduction in the composite endpoint will likely imply a reduction in each of its components. However, to confirm concordance of the effect of the intervention each component of the composite outcome will be reported independently as secondary outcome. Thirdly, each component outcome is prespecified, well defined, and has the potential to be influenced by the treatment. Importantly, the composite endpoint proposed is more inclusive of relevant clinical findings than any of the available data in the literature to date. At present the best quality data used for the AUA and EAU recommendations is based on a synthesis of several relatively small, methodologically inferior trials. Existing trials report very heterogeneous outcomes. Few studies report poorly defined "symptomatic UTI", while most trials simply report the occurrence of asymptomatic bacteriuria only, at a cutoffs which range from $\geq 10^3$ to $\geq 10^5$ CFU/ml[15-17] .

Another potential criticism of our proposed RCT is the use of the IPSS as a secondary outcome, since it has not been validated for the evaluation of UTI in men and women. Unfortunately, there are no standardized questionnaires that have been validated in either gender for UTI diagnosing. If antibiotic prophylaxis reduces the incidence of symptomatic cystitis, we feel it is important to determine if it consequently reduces LUTS and improve patient quality of life. The IPSS is the most often used quality of life measure and assessment tool for lower urinary tract symptoms and would provide this data in our RCT. We recognize that the IPSS may not be the ideal tool in this setting and should be viewed as an exploratory outcome for this study.

The principal strength of our study is that it is a large blinded RCT. RCT design controls for known and unknown confounders, and allows for a clearer assessment of antibiotic prophylaxis in the setting of SWL. The proposed RCT will also be the largest and most methodologically robust trial investigating the use of antibiotic prophylaxis to date[13,14,15]. As well, we propose to evaluate a simple antibiotic protocol which can be easily generalized and adopted at any institution. Therefore it is reasonable to expect that the results of this study, whether positive or negative, will have significant global impact on recommendations for the use of pre-SWL antibiotics.